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| EXAMINER | |
|---|---|
| WINKLER, ULRIKE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/930,619 | CUNANAN ET AL. | |
| | Examiner | Art Unit | |
| | Ulrike Winkler | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24,28 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,28 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/6/04; 6/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The Amendment filed January 13, 2004 in response to the Office Action of August 13, 2003 is acknowledged and has been entered. Claims 25-27 and 29-49 have been cancelled. Claims 1-24, 28, 50-53 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 1-25 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of Applicant's amendment to the claims.

The rejection of claims 1-25 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained**. Although applicants have attempted to provide method steps to overcome the prior rejection, there are still critical methods steps missing. The claim are now drawn to a method of eliminating 75% of the binding sites (which are defined as phospholipid, protein and/or polysaccharide) from a biological material wherein the method steps comprise: washing the biological material at least 2x or until greater than 75% of the

binding site is removed, separating the wash solution from the biological material, determining the presence of binding site in the separated washed material, wherein the biological material retains its structural integrity. The critical method step that is lacking is having a way to correlate that 75% of the binding site removed is removed from the biological material by only measuring the presence of the binding site in the wash solution (an aliquot of a preparation).

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

***Claim Rejections - 35 USC § 102***

The rejection of claims 1-15, 19, 21, 23, 25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (U.S. Pat. No. 6,008,292) **is withdrawn** in view of Applicant's amendment.

The rejection of claims 1-15, 17, 19, 21, 23, 25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Nashef (U.S. Pat. No. 4,729,139) **is withdrawn** in view of Applicant's amendment.

The rejection of claims 1-4, 18 and 20-25 under 35 U.S.C. 102(e) as being anticipated by Abraham et al. (U.S. Pat. No. 6,599,690) **is withdrawn** in view of Applicant's amendment.

The rejection of claims 1, 3, 4, 11, 19, 23, 25 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Girardot et al. (U.S. Pat. No. 6,521,179) **is withdrawn** in view of Applicant's amendment.

The rejection of claims 1-4, 14-16, 18-25 under 35 U.S.C. 102(a) or (e) as being anticipated by Mirsch et al. (U.S. Pat. No. 6,121,041) **is withdrawn** in view of Applicant's amendment.

The rejection of claims 1-4, 14, 15, 17 under 35 U.S.C. 102(b) as being anticipated by Vyavahare et al. (Circulation, 1997) **is withdrawn** in view of Applicant's amendment.

The rejection of claims 1-15, 17-25 and 28 under 35 U.S.C. 102(a) or (e) as being anticipated Cunanan et al. (U.S. Pat. No. 6,214,054) as evidenced by Vyavahare et al. (Circulation, 1997) **is withdrawn** in view of Applicant's amendment.

***Double Patenting***

The rejection of claims 1-15, 17-24, 28 and added claims 50-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,214,054 in view of Vyavahare et al. (Circulation, 1997) **is maintained**.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the method disclosed in U.S. Patent No. 6,214,054 will result in the removal of phospholipid form the fixed bioprosthetic tissue, as evidenced by Vyavahare et al. where

phospholipid removal was achieved with ethanol treatment of glutaraldehyde fixed bioprosthetic tissue (Vyavahare et al., Circulation, Table 1).

Applicant's arguments have been fully considered but are not deemed persuasive, because the treatment set out in U.S. Patent No. 6,214,054 would remove 75% of the phospholipid binding-site from the biological material with the need of adding an additional washing step using the same solution would be an obvious step. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235
(CCPA 1955). "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In this instance the use of ethanol treatment of the biological material is the result-effective variable, because ethanol that has been shown by Vyavahare et al. to remove the phospholipid from the biological sample. Repeating a step that contains ethanol would give the predicable result of removing more of the phospholipid from the sample. Therefore, the instant rejection is maintained.

New Rejection:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24, 50-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant amendment adds the term "aliquot" or "aliquot of a preparation" there is no written description for "aliquot" in the specification.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15, 17-24, 28 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunanan et al. (U.S. Pat. No. 6,214,054) in view of Vyavahare et al. (Circulation, 1997).

The instant invention is drawn to a method of eliminating or reducing the "binding site" in a biological. Any method that removes protein or cellular debris from a biological material would fall within the scope of the claim, by removing the undefined binding sites (which can be made up of phospholipids, proteins and glycoproteins). The method utilizes a surfactant or denaturation agent or both, the surfactant is Tween 80 and the denaturation agent is an alcohol such as ethanol or isopropanol. By removing the "binding site" unwanted proteins are prevented or inhibited from binding. The method also requires treating the biological sample with a cross-linking agent, such as an aldehyde. Any method that removes protein, lipids and/or cellular debris from a biological material would fall within the scope of the claims by removing binding sites. For purposes of the instant rejections the term "binding site" in interpreted to be cells and cellular debris which are comprised of phospholipid, protein and polysaccharide components. The amended claims indicate that the biological material is treated two or more time with the cleaning solution.

Cunanan et al. teaches a method of preparing bioprosthetic tissue (see claims) using a solution which is a combination of formaldehyde, ethanol and Tween (see claim 16) for the processing of the tissue. The reference does not teach measuring the amount removal of the binding site from the biological material. The reference does not teach repeating the cleaning step.

Vyavahare et al. teaches that ethanol treatment is effective at removing phospholipids from tissue (see table 1). The reference teaches measuring the effective removal of the binding site from the biological material.

It would have been obvious to one of ordinary skill in the art to repeat the treatment of the biological material with the solution containing detergent, protic solvent and a cross linking agent. "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In this instance the use of ethanol treatment of the biological material is the result-effective variable, because ethanol that has been shown by Vyavahare et al. to remove the phospholipid from the biological sample. Repeating a step that contains ethanol would give the predicable result of removing more of the phospholipid from the sample. One having ordinary skill in the art would have had a high expectation of success in removing the phospholipid from the biological material by subjecting the martial to multiple washes using the cleaning solution. Therefore, the instant invention is obvious over Cunanan et al. in view of Vyavahare et al.

Claims 1-15, 17-24, 28 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (U.S. Pat. No. 6,008,292) and Vyavahare et al. (Circulation, 1997).

The instant invention is drawn to a method of eliminating or reducing infection in a biological material by removing "binding sites" found in the biological material. Any method that removes protein or cellular debris from a biological material would fall within the scope of

the claim, by removing the undefined binding sites. The method utilizes a surfactant or denaturation agent or both, the surfactant is Tween 80 and the denaturation agent is an alcohol such as ethanol or isopropanol (claims 5-10, 17, 28). By removing the "binding site" unwanted proteins are prevented or inhibited from binding (claims 21 and 22). The method also requires treating the biological sample with a cross-linking agent, such as an aldehyde (claims 11-13). Any method that removes protein, lipids and/or cellular debris from a biological material would fall within the scope of the claims by removing binding sites. For purposes of the instant rejections the term "binding site" in interpreted to be cells and cellular debris which are comprised of phospholipid, protein and polysaccharide components.

Lee et al. teaches a method of preparing collagenous biological material by treating the tissue with Denacol and 20% ethanol as well as treating tissue with a mixture of glutaraldehyde, ethanol and Tween-80 (see example 1). The tissue is then treated with polyglycidyl ether either in conjunction or following the glutaraldehyde treatment (see example 1). Ethanol and Tween agents known to be capable of solubelizing phospholipids. Glutaraldehyde is a well-known sterilization/disinfecting agent. The reference does not teach repeating a treatment step.

Vyavahare et al. teaches that ethanol treatment is effective at removing phospholipids from tissue (see table 1). The reference teaches measuring the effective removal of the binding site from the biological material using ethonal.

It would have been obvious to one of ordinary skill in the art to repeat the treatment of the biological material with the solution containing detergent, protic solvent and a cross linking agent. "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the

optimum combination of percentages." *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In this instance the use of ethanol treatment of the biological material is the result-effective variable, because ethanol that has been shown by Vyavahare et al. to remove the phospholipid from the biological sample. Repeating a step that contains ethanol would give the predicable result of removing more of the phospholipid from the sample. One having ordinary skill in the art would have had a high expectation of success in removing the phospholipid from the biological material by subjecting the martial to multiple washes using the cleaning solution. Therefore, the instant invention is obvious over Lee et al. and Vyavahare et al.

Claims 1-24, 28 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirsch et al. (U.S. Pat. No. 6,121,041) and Girardot et al. (U.S. Pat. No. 6,521,179)

The instant invention is drawn to a method of eliminating or reducing infection in a biological material by removing "binding sites" found in the biological material. Any method that removes protein or cellular debris from a biological material would fall within the scope of the claim, by removing the undefined binding sites. The method utilizes a surfactant or denaturation agent or both, the surfactant is Tween 80 and the denaturation agent is an alcohol such as ethanol or isopropanol (claims 5-10, 17, 28). By removing the "binding site" unwanted proteins are prevented or inhibited from binding (claims 21 and 22). The method also requires

treating the biological sample with a cross-linking agent, such as an aldehyde (claims 11-13). Any method that removes protein, lipids and/or cellular debris from a biological material would fall within the scope of the claims by removing binding sites. For purposes of the instant rejections the term "binding site" in interpreted to be cells and cellular debris which are comprised of phospholipid, protein and polysaccharide components.

Mirsch et al. teaches a method of decellularizing tissue using microorganism while leaving the matrix intact, the microorganism are subsequently inactivated (see claims 1 and 7). Subsequent processing can be used to remove the microorganism (see column 9, line 10-24). Because the art teaches the decellularizing of the bioprosthetic tissue, the "binding sites" found in the cellular material are removed. The reference does not teach the repeating the step which included the addition of the microorganism that is used to digest any tissue on the bioprosthetic material. The reference does not quantify the removal after the addition the microorganism for digesting the tissue, it deemed complete when the only thing left is the collagenous material.

Girardot et al. (U.S. Pat. No. 6,521,179) teaches a method of sterilizing tissue prostheses and tissue valves. The reference provides a process of sterilization of biological tissue that has been rendered acellular either before or after cross-linking (see summary of invention). Pericardial tissue is sterilized using 25 mM EDC, 10 mM Hepes, 0.85% NaCl, 20% isopropyl alcohol, EDC is a water soluble coupling agent. The reference teaches the method steps of treating with a cross-linking agent EDC and an alcohol at concentrations effective to kill microorganisms (see claim 1). The reference does not teach repeating a step or specifically measuring the reduction of the binding site in the biological material.

It would have been obvious to one of ordinary skill in the art to repeat the treatment of the biological material with the microorganism that result in the removal of the cellular martial which contain the "binding site". "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In this instance the use of microbial treatment of the biological material is the result-effective variable, because is decellularizes the biological material. Repeating a step that deculalrises a biological material will only result in a martial that contain no cells and therefore no "binding sites". One having ordinary skill in the art would have had a high expectation of success in sterilizing the biological material that has been rendered acellular using the methods of Mirsh et al. following the method of Girardot et al. Therefore, the instant invention is obvious over Mirsh et al. and Girardot et al.

Claims 1-15, 17-24, 28 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abraham et al. (U.S. Pat. No. 6,599,690) in view of Shenoy et al. (U.S. Pat. No. 5,756,678)

The instant invention is drawn to a method of eliminating or reducing infection in a biological material by removing "binding sites" found in the biological material. Any method that removes protein or cellular debris from a biological material would fall within the scope of

the claim, by removing the undefined binding sites. The method utilizes a surfactant or denaturation agent or both, the surfactant is Tween 80 and the denaturation agent is an alcohol such as ethanol or isopropanol (claims 5-10, 17, 28). By removing the "binding site" unwanted proteins are prevented or inhibited from binding (claims 21 and 22). The method also requires treating the biological sample with a cross-linking agent, such as an aldehyde (claims 11-13). Any method that removes protein, lipids and/or cellular debris from a biological material would fall within the scope of the claims by removing binding sites. For purposes of the instant rejections the term "binding site" in interpreted to be cells and cellular debris which are comprised of phospholipid, protein and polysaccharide components.

Abraham et al. teaches a method of cleansing/treating tissue to obtain collagenous tissue and remove non-collagenous components such as cells, cellular debris, proteoglycans and glycosaminoglycans, by treatment with alkali, chelating agents and acids (see claim 1 and examples 1-9). Because cellular material and protein is removed in the processing steps disclosed by Abraham et al. infectious agents and binding site for the infectious agent are removed in the process as well. The reference teachers repeating the washing step, the reference does not teach repeating the active steps that result in the cellular material and protein being removed which is the acid and hydroxide wash. The reference does teach detecting the quality of the treatment by verifying the percentage of collagen present in the sample after the treatment and comparing it to non-treated sample (see column 18, lines 1-8) or determining the amount of lipid present after the treatment procedure (see column 16, lines 15-49).

Shenoy et al. teach the removal of prion from a collagenous mixture by treating the mixture with a hydroxide containing solution.

It would have been obvious to the ordinary artisan tat the time the invention was made that the treatment of the collagenous biological material as taught by Abrams et al. would result in the removal of prion as taught by Shenoy et al. Abram et al teaches repeating the washing step to remove residual treating solution. It would have been obvious to the ordinary artisan to repeat the treatment with the active ingredients in order to obtain a biological material in which more of the non-collagenous components "binding sites" have been removed. "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In this instance the use of microbial treatment of the biological material is the result-effective variable, because is decellularizes the biological material. Repeating a step that deculalrises a biological material will only result in a martial that contains no cells and therefore no "binding sites". One having ordinary skill in the art would have had a high expectation of success in of removing the residual non-collagenous material from the biological material by repeating the active cleansing steps as taught by Abraham et al. One having ordinary skill in the art would have had a high expectation that the treatment steps of Abraham et al. lead to the inactivation of the prion as taught by Shenoy et al. Therefore, the instant invention is obvious over Abraham et al. in view of Shenoy et al.

***Conclusion***

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 4/2/04